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Synthesis of 1,3,3-trimethyl- and 1,2,3,3-tetramethyl-5-(methyl- and dimethyl-carbamoyloxy) indolines and their methiodides

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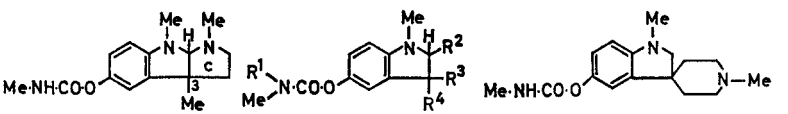
The title compounds have been synthesised for testing as anticholinesterases.

FOLLOWING the observation that the anticholinesterase activity of the alkaloid physostigmine (eserine) (I) is dependent upon the



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presence of the methylcarbamoyloxy group and the basic nitrogen atom, many compounds incorporating these two features, and also those with a dimethylcarbamoyloxy group in place of a methylcarbamoyloxy group, and with a quaternary instead of a tertiary nitrogen atom, were synthesised and their anticholinesterase activity investigated (for a review of synthetic analogues of physostigmine see Stempel & Aeschlimann, 1956).

The first synthetic anticholinesterases incorporating a 5-hydroxyindoline nucleus and omitting ring C of physostigmine (I), 5-dimethylcarbamoyloxy-1,2,3-trimethylindoline (II; $R^1 = R^2 = R^3 = Me$, $R^4 = H$) and its methiodide, were prepared by Gardner & Stevens (1947). Later, Kolosov & Preobrazhenskii (1953) synthesised 1-methyl-5-methylcarbamoyloxy (II; $R^1 = R^2 = R^3 = R^4 = H$) and 1,3-dimethyl-5(methyl- and dimethyl-carbamoyloxy)indoline (II; $R^2 = R^4 = H$, $R^3 = Me$, $R^1 = H$ and Me respectively) and their methiodides. Pharmacological tests indicated that all these 5-hydroxyindoline derivatives are anticholinesterases. Another 5-hydroxyindoline derivative (III) has also been synthesised and found to possess only weak anticholinesterase activity (Kretz, Müller & Schlittler, 1952).

Whereas C-3 in the indoline nucleus of physostigmine (I) is quaternary, the corresponding atom in the above-mentioned synthetic analogues of structure (II) is secondary or tertiary. We have now prepared, by the route shown in scheme 1, the corresponding 5-hydroxyindoline derivatives (mentioned in the title) in which C-3 of the indoline nucleus is quaternary.

Fischer indolisation (for a recent review see Robinson, 1963) of isobutyraldehyde *p*-benzyloxyphenylhydrazone (IV; R = H) and isopropyl methyl ketone *p*-benzyloxyphenylhydrazone (IV; R = Me) using 25% aqueous ethanolic acetic acid as catalyst gave respectively the 3*H*-indoles (V; R = H) and (V; R = Me). As expected from previous observations

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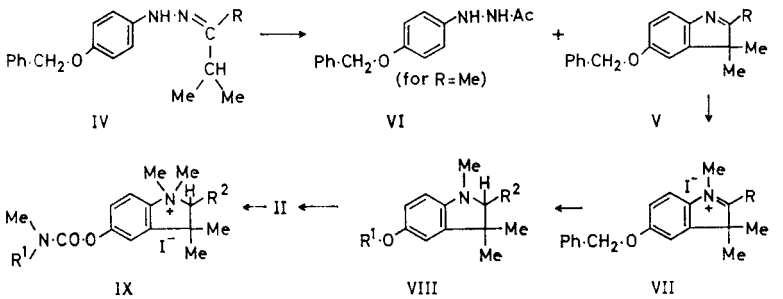

Scheme 1

(for references see Robinson, 1963), no 5-benzyloxy-2-isopropylindole, which would result from the alternative direction of indolisation in IV (R = Me), could be isolated from the second indolisation. A by-product was, however, isolated from this reaction and was shown (see Experimental) to be *N'-p*-benzyloxyphenylacethydrazide (VI). Quaternisation of (V; R = H and Me) with methyl iodide gave the corresponding methiodides (VII; R = H and Me), which upon reduction with sodium borohydride gave the corresponding indolines (VIII; R^1 = Ph·CH_2, R^2 = H and Me). Debenzylation was then effected by hydrogenolysis at room temperature and pressure using 10% palladium-upon-charcoal as catalyst to give (VIII; R^1 = H, R^2 = H and Me). Treatment of these two phenols with methyl isocyanate in the presence of a trace of sodium (cf. Kolosov & Preobrazhenskii, 1957) then gave the required methylurethanes (II; R^1 = H, R^3 = R^4 = Me, R^2 = H and Me), which with methyl iodide were converted into the corresponding methiodides (IX; R^1 = H, R^2 = H and Me). Reaction of the phenols with dimethylcarbamoyl chloride in dry pyridine (cf. Kolosov & Preobrazenskii, 1957) gave the dimethylurethanes (II; R^1 = R^3 = R^4 = Me, R^2 = H and Me), isolated as the crystalline hydrochlorides. Reaction of the free bases, liberated from the hydrochlorides, with methyl iodide afforded the methiodides (IX; R^1 = Me, R^2 = H and Me).

Experimental

Melting-points were recorded on a Kofler hot-stage apparatus and are uncorrected. Ultraviolet spectra were measured in ethanolic solution, unless otherwise stated, on a Unicam SP 800 spectrophotometer, and infrared spectra as Nujol mulls on a Unicam SP 200 spectrophotometer. The proton magnetic resonance spectrum was recorded in deuterochloroform solution on a Varian A 60 spectrometer using tetramethylsilane as internal standard. Solutions were dried with anhydrous magnesium sulphate, and solvents were removed on a steam-bath under reduced pressure (water-pump).

5-Benzyloxy-3,3-dimethyl-3H-indole (V; R = H). *p*-Benzyloxyphenylhydrazine hydrochloride (Mentzer, Beaudet & Bory, 1953) (15 g) was suspended in 25% aqueous acetic acid (600 ml) and isobutyraldehyde (5 g) was added. The mixture was then boiled under reflux for 1 hr when

a dark-brown oil separated. Ethanol (300 ml) was then added and the resulting clear brown solution was boiled under reflux for a further 5 hr. The ethanol was removed, and water (2·5 litres) was added to the aqueous acidic residue. The liberated oil was taken into ether (4 × 500 ml), the combined ethereal solutions were extracted with 3N hydrochloric acid (3 × 300 ml), the combined acidic extracts were basified by the addition of sodium hydroxide pellets (ice also added) and the liberated oil was taken into ether (3 × 300 ml). After drying the combined ethereal solutions, removal of the solvent afforded the 3H-*indole* (V; R = H) as a tan-coloured crystalline solid (5·53 g; 37%), m.p. 98–99°. A small sample was recrystallised from aqueous ethanol to afford cream-coloured needles, m.p. 98–100°. Found: C, 81·3; H, 6·6. $C_{17}H_{17}NO$ requires C, 81·2; H, 6·7%. λ_{max} 218, 278 λ_{min} 244 mμ (log ε 4·09, 3·97 and 3·51 respectively); λ_{max} 248·5, 322 λ_{min} 235, 268–269 mμ (log ε 4·00, 3·97, 3·85 and 3·39 respectively in concentrated hydrochloric acid) (ultraviolet absorption of 3*H*-indole and 3*H*-indole cation chromophores respectively).

The above 3*H*-indole (5·3 g), without purification by recrystallisation, was dissolved in methyl iodide (20 ml). After standing at room temperature for 6 days, the crystals which had been deposited from the reaction mixture during this time were collected and washed with ether to afford the *methiodide* (VII; R = H) as pale-yellow prisms (2·45 g; 30%), m.p. 142–144°. Recrystallisation from ethanol-ether gave pale-yellow plates, m.p. 146–147°. Found: C, 55·2; H, 5·1. $C_{18}H_{20}INO$ requires C, 54·9; H, 5·1%.

5-*Benzyloxy*-2,3,3-*trimethyl*-3H-*indole* (V; R = Me). This was prepared from *p*-benzyloxyphenylhydrazine hydrochloride (Mentzer, Beaudet & Bory, 1953) (15 g) and isopropyl methyl ketone (6·0 g) following a method analogous to that described above for the preparation of 5-benzyloxy-3,3-dimethyl-3*H*-indole (V; R = H). On removal of the solvent from the dried ethereal solution of the basic product, the 3H-*indole* (V; R = Me) was obtained as a grey-brown solid (9·85 g; 62%), m.p. 94–96°. Recrystallisation of a small sample from aqueous ethanol afforded buff-coloured needles, m.p. 96–98°. Found: C 81·7; H 7·3. $C_{18}H_{19}NO$ requires C, 81·5; H, 7·1%. λ_{max} 219, 272 λ_{min} 241 mμ (log ε 4·06, 4·00, and 3·49 respectively); λ_{max} 244, 312 λ_{min} 235, 263·5 mμ (log ε 3·79, 3·78, 3·71 and 3·28 respectively in concentrated hydrochloric acid) (ultraviolet absorption of 3*H*-indole and 3*H*-indole cation chromophores respectively).

The ethereal solution remaining after extraction with 3N hydrochloric acid was washed with aqueous sodium carbonate solution, dried, evaporated to about 5 ml, and cooled. The crystalline deposit was collected and washed with a little ether to give VI as golden-yellow plates (0·49 g; 3·5%), m.p. 156–160°. Recrystallisation from ethanol afforded glistening yellow plates, m.p. 158–160°. Found: C, 70·05; H, 6·2. $C_{15}H_{16}N_2O_2$ requires C, 70·3; H, 6·2%. ν_{max} 3290 ± 10 m and 3200 ± 10 m (N–H stretching) and 1660 ± 3 ms (amide C = O stretching) cm^{-1}. τ = 5·03 (2-proton singlet) (benzyloxy methylene protons) and 8·00 (3-proton singlet) (acetyl group methyl protons).

The 3*H*-indole (V; R = Me) (9·65 g), without purification by recrystallisation, was dissolved in ether (100 ml), methyl iodide (20 ml) was added, and the solution was stood at room temperature. After 3 days the crystalline precipitate was collected and washed with ether to give the *methiodide* (VII; R = Me) as tan-coloured needles (12·0 g; 81·5%), m.p. 206–207°. Recrystallisation from ethanol-ether gave pale-yellow plates, m.p. 207–208°. Found: C, 56·0; H, 5·3. $C_{19}H_{22}INO$ requires C, 56·0; H, 5·4%.

5-*Benzyloxy*-1,3,3-*trimethylindoline* (VIII; $R^1 = Ph{\cdot}CH_2$, $R^2 = H$). To a solution of 5-benzyloxy-3,3-dimethyl-3*H*-indole methiodide (VII; R = H) (2·3 g) in methanol (70 ml) was added finely powdered sodium borohydride (1·5 g) in small quantities over a period of about 5 min with gentle swirling. After addition was complete the reaction mixture was kept at room temperature for 2 hr, water (100 ml) was added, and the crystalline precipitate was collected, washed with water and dried (P_2O_5–vacuum desiccator) to give the *indoline* (VIII; $R^1 = Ph{\cdot}CH_2$, $R^2 = H$) as white plates (1·45 g; 93%), m.p. 46–48°, unchanged by recrystallisation from aqueous ethanol. Found: C, 81·2; H, 8·2. $C_{18}H_{21}NO$ requires C, 80·9; H, 7·85%. λ_{max} 250, 311–312 λ_{min} 225·5, 285 mμ (log ϵ 3·98, 3·46, 3·64 and 3·10 respectively) (ultraviolet absorption of indoline chromophore).

5-*Benzyloxy*-1,2,3,3-*tetramethylindoline* (VIII; $R^1 = Ph{\cdot}CH_2$, $R^2 = Me$). 5-Benzyloxy-2,3,3-trimethyl-3*H*-indole methiodide (VII; R = Me) (10·0 g) was similarly reduced with sodium borohydride (5·0 g) in methanol (220 ml), the *indoline* (VIII; $R^1 = Ph{\cdot}CH_2$, $R^2 = Me$) being obtained as white plates (6·8 g; 98%), m.p. 58–59°, unchanged by recrystallisation from aqueous ethanol. Found: C, 81·25; H, 8·2. $C_{19}H_{23}NO$ requires C, 81·1; H, 8·2%. λ_{max} 249, 312–313 λ_{min} 226, 285 mμ (log ϵ 4·02, 3·47, 3·66 and 3·10 respectively) (ultraviolet absorption of indoline chromophore).

1,3,3-*Trimethyl*-5-*methylcarbamoyloxyindoline* (II; $R^1 = R^2 = H$, $R^3 = R^4 = Me$). 5-Benzyloxy-1,3,3-trimethylindoline (VIII; $R^1 = Ph{\cdot}CH_2$, $R^2 = H$) (1·55 g) dissolved in commercial absolute ethanol (100 ml) was hydrogenolysed at room temperature and pressure in the presence of 10% palladium-on-charcoal catalyst (0·5 g). After 7 hr, when hydrogenolysis was complete, the catalyst was removed by rapid filtration and the filtrate evaporated to give 5-*hydroxy*-1,3,3-*trimethylindoline* (VIII; $R^1 = R^2 = H$) as a viscous gum (0·95 g; 95%) which soon completely crystallised (recrystallisation and characterisation was not effected owing to the rapid decomposition of the compound on exposure to air). The phenolic product (0·80 g) was dissolved in dry ether (60 ml) and sodium (about 1 mg) was added, followed by methyl isocyanate (3 ml). After standing at room temperature for 3 days with occasional shaking, the reaction mixture was filtered and the filtrate evaporated to give the *methylurethane* (II; $R^1 = R^2 = H$, $R^3 = R^4 = Me$) as a red-coloured gum (0·95 g; 89·5%) which soon completely crystallised. Recrystallisation from ether afforded grey-white prisms (0·55 g), m.p. 122–124°. Found: C, 66·55; H, 7·4. $C_{13}H_{18}N_2O_2$ requires C, 66·6; H, 7·7%. ν_{max} 1703 $\pm$ 3 ms (C = O stretching) and 3370 $\pm$ 10 m (N–H stretching) cm^{-1}.

To the mother liquor from the recrystallisation in ether (15 ml) was added methyl iodide (4 ml). After standing for 6 days at room temperature the crystalline deposit which had slowly formed was collected and washed with ether to give the *methiodide* (IX; $R^1 = R^2 = H$) as tan-coloured prisms (0·61 g; 94·5%), m.p. 186–189°. Recrystallisation from ethanol afforded buff-coloured prisms, m.p. 196–197°. Found: C, 44·9; H, 5·7. $C_{14}H_{21}IN_2O_2$ requires C, 44·7; H, 5·6%.

1,2,3,3-*Tetramethyl*-5-*methylcarbamoyloxyindoline* (II; $R^1 = H$, $R^2 = R^3 = R^4 = Me$). 5-Benzyloxy-1,2,3,3-tetramethylindoline (VIII; $R^1 = Ph{\cdot}CH_2$, $R^2 = Me$) (7·3 g) dissolved in commercial absolute ethanol (150 ml) was hydrogenolysed, by the method described above for the hydrogenolysis of 5-benzyloxy-1,3,3-trimethylindoline (VIII; $R^1 = Ph{\cdot}CH_2$ $R^2 = H$), to give a quantitative yield of 5-*hydroxy*-1,2,3,3-*tetramethylindoline* (VIII; $R^1 = H$, $R^2 = Me$) as a light-brown viscous oil which completely crystallised. A small sample was recrystallised from ether to give tan-coloured prisms, m.p. 104–109°. Found: C, 75·2; H, 9·0. $C_{12}H_{17}NO$ requires C, 75·4; H, 8·9%. The phenol was then converted into the *methylurethane* (II; $R^1 = H$, $R^2 = R^3 = R^4 = Me$) in 94% yield, following a procedure similar to that described above, the product being recrystallised from ether-light petroleum (b.p. 40–60°) to give cream-coloured prisms, m.p. 110–112°. Found: C, 67·8; H, 8·4. $C_{14}H_{20}N_2O_2$ requires C, 67·75; H, 8·05%. ν_{max} 1704 ± 3 s (C = O stretching) and 3410 ± 10 m (N—H stretching) cm^{-1}.

The methylurethane (3·2 g) was dissolved in ether (150 ml), methyl iodide (15 ml) was added, and after standing at room temperature for 8 days, the *methiodide* (IX; $R^1 = H$, $R^2 = Me$) (2·67 g; 53%) which had deposited was collected. Recrystallisation from ethanol-ether afforded cream-coloured prisms, m.p. 168–171°. Found: C, 46·25; H, 6·2; $C_{15}H_{23}IN_2O_2$ requires C, 46·15; H, 5·9%.

5-*Dimethylcarbamoyloxy*-1,3,3-*trimethylindoline hydrochloride* (II; $R^1 = R^3 = R^4 = Me$, $R^2 = H$) HCl. 5-Hydroxy-1,3,3-trimethylindoline (VIII; $R^1 = R^2 = H$) (1·50 g) (prepared as described above) was dissolved in dry pyridine (10 ml), dimethylcarbamoyl chloride (4·0 g) was added, and the mixture was heated at 140–150° for 3 hr. After cooling, the reaction mixture was evaporated to dryness, water (10 ml) was added, and the mixture again evaporated. After repeating this operation a further three times, the brown gummy residue was partitioned between ether (100 ml) and 10% aqueous potassium hydroxide solution (15 ml). After drying, the ethereal solution was evaporated to leave a brown oil. This was dissolved in ethanol (10 ml), 20% hydrochloric acid (2·5 ml) was added, and the solution was evaporated to afford a viscous gum which crystallised on trituration with methanol-ether to give the hydrochloride of the *dimethylurethane* (II; $R^1 = R^3 = R^4 = Me$, $R^2 = H$) as yellow prisms (1·15 g; 45%), m.p. 110–112°. Recrystallisation from methanol-ether afforded pale-yellow prisms, m.p. 111–112°. Found: C, 58·85; H, 7·6. $C_{14}H_{21}ClN_2O_2$ requires C, 59·1; H, 7·3%. ν_{max} 1736 ± 3 ms (C = O stretching) and 2250 ± 10 m, broad ($N^+ - H$ stretching) cm^{-1}.

The hydrochloride (0·50 g) was treated with an excess of cold aqueous

saturated sodium bicarbonate solution, the liberated base was taken into ether (2 × 100 ml), the combined ethereal solutions were dried, and evaporated to about 10 ml. Methyl iodide (10 ml) was added and after 6 days the crystalline deposit (0·60 g; 88%) which had gradually formed was collected. Recrystallisation from ethanol-ether afforded the *methiodide* (IX; R^1 = Me, R^2 = H) as pale-yellow needles, m.p. 172–176°. Found: C, 46·0; H, 6·0. $C_{15}H_{23}IN_2O_2$ requires C, 46·1; H, 5·8%.

5-*Dimethylcarbamoyloxy*-1,2,3,3-*tetramethylindoline hydrochloride* (II; R^1 = R^2 = R^3 = R^4 = Me) HCl. Similarly, 5-hydroxy-1,2,3,3-tetramethylindoline (VIII; R^1 = H, R^2 = Me) was converted into the hydrochloride of its *dimethylurethane* (II; R^1 = R^2 = R^3 = R^4 = Me) in 66% yield. The *hydrochloride*, initially obtained as a gum, completely crystallised on standing *in vacuo* overnight over potassium hydroxide pellets. Recrystallisation from commercial absolute ethanol afforded white needles, m.p. 138–140°. Found: C, 60·15; H, 7·5. $C_{15}H_{23}ClN_2O_2$ requires C, 60·25; H, 7·7%. ν_{max} 1727 ± 3 s (C = O stretching) and 2130 ± 10 s, broad (N^+ — H stretching) cm^{-1}.

The *free base*, liberated from the hydrochloride, was converted into the *methiodide* (IX; R^1 = R^2 = Me) in 57% yield by the method described above to prepare the methiodide (IX; R^1 = Me, R^2 = H) from the corresponding hydrochloride. Recrystallisation from ethanol-ether afforded buff-coloured prisms, m.p. 180–181°. Found: C, 47·8; H, 6·4. $C_{16}H_{25}IN_2O_2$ requires C, 47·5; H, 6·1%.

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